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ORIGINAL INVESTIGATIONS

Safety and Efficacy of the Totally Subcutaneous Implantable Defibrillator

2-Year Results From a Pooled Analysis of the IDE Study and EFFORTLESS Registry

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ABSTRACT

BACKGROUND The entirely subcutaneous implantable cardioverter-defibrillator (S-ICD) is the first implantable defibrillator that avoids placing electrodes in or around the heart. Two large prospective studies (IDE [S-ICD System IDE Clinical Investigation] and EFFORTLESS [Boston Scientific Post Market S-ICD Registry]) have reported 6-month to 1-year data on the S-ICD.

OBJECTIVES The objective of this study was to evaluate the safety and efficacy of the S-ICD in a large diverse population.

METHODS Data from the IDE and EFFORTLESS studies were pooled. Shocks were independently adjudicated, and complications were measured with a standardized classification scheme. Enrollment date quartiles were used to assess event rates over time.

RESULTS Eight hundred eighty-two patients who underwent implantation were followed for 651 ± 345 days. Spontaneous ventricular tachyarrhythmia (VT)/ventricular fibrillation (VF) events (n = 111) were treated in 59 patients; 100 (90.1%) events were terminated with 1 shock, and 109 events (98.2%) were terminated within the 5 available shocks. The estimated 3-year inappropriate shock rate was 13.1%. Estimated 3-year, all-cause mortality was 4.7% (95% confidence interval: 0.9% to 8.5%), with 26 deaths (2.9%). Device-related complications occurred in 11.1% of patients at 3 years. There were no electrode failures, and no S-ICD–related endocarditis or bacteremia occurred. Three devices (0.3%) were replaced for right ventricular pacing. The 6-month complication rate decreased by quartile of enrollment (Q1: 8.9%; Q4: 5.5%), and there was a trend toward a reduction in inappropriate shocks (Q1: 6.9% Q4: 4.5%).

CONCLUSIONS The S-ICD demonstrated high efficacy for VT/VF. Complications and inappropriate shock rates were reduced consistently with strategic programming and as operator experience increased. These data provide further evidence for the safety and efficacy of the S-ICD. (Boston Scientific Post Market S-ICD Registry [EFFORTLESS]; NCT01085435; S-ICD® System IDE Clinical Study; NCT01064076) (J Am Coll Cardiol 2015;65:1605–15) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ATP = antitachycardia pacing

S-ICD = subcutaneous implantable cardioverter-defibrillator

MVT = monomorphic ventricular tachyarrhythmia

SVA = supraventricular arrhythmia

TV-ICD = transvenous implantable cardioverter-defibrillator

VF = ventricular fibrillation

VT = ventricular tachyarrhythmia

The entirely subcutaneous implantable cardioverter defibrillator (S-ICD) is an alternative to transvenous implantable cardioverter-defibrillators (TV-ICDS) for the prevention of sudden cardiac death (1–4). The first pilot phase human studies of the S-ICD commenced in 2008, followed by subsequent regulatory (1,2) and post-market studies (3,4). Two studies took place to track the initial worldwide experience with the S-ICD (2,3). The EFFORTLESS (Boston Scientific Post Market S-ICD Registry) trial (3) began enrollment in 2009 and continues to collect demographic, safety, and efficacy data. The IDE (S-ICD System IDE Clinical Investigation) study began enrolling in 2009 and collected the same information as the EFFORTLESS trial. The 6-month to 1-year data for each of these trials were reported separately, with both demonstrating safety and efficacy (2,3).

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Because of the relatively low rate of adverse events reported in the individual trials, combining these 2 studies provided a unique opportunity to evaluate complications and to collect a significant number of spontaneous events to evaluate the safety and efficacy of the S-ICD system over a longer follow-up period and in a larger group of subjects. The aim of this study is to present the world-wide experience with the S-ICD at a mean of 22-month follow-up by pooling these databases.

METHODS

STUDY COHORT. The study designs and endpoints were similar, enabling this pooled analysis (**Figure 1**). The pooled database consisted of 568 patients from the EFFORTLESS registry (3), 308 from the IDE study (2), and 13 patients from both studies, giving a total of 889 patients who underwent an implantation procedure. Complications were evaluated in all patients who underwent an implantation procedure. Seven patients underwent an implantation procedure, but they were not discharged with a device in the IDE study due to acute ventricular fibrillation (VF) test results, which left an implantation patient cohort of 882. Data were collected until May 21, 2013 for the ongoing EFFORTLESS registry.

Poolability of data across studies was assessed by analysis of incidence of complications, appropriate and inappropriate shocks, conversion efficacy, and mortality. In outcomes that differed by study, exploratory analysis was performed to explain the differences between studies.

Approval for both studies was obtained by local ethics or institutional review boards, and informed consent was obtained from all patients.

Device programming was determined at the discretion of the physician who performed the procedure and was not controlled during the implantation or study durations. The device programming features included 2 possible tachyarrhythmia detection zones: 1) the shock only zone, in which detection and therapy were based on rate only; and 2) an additional conditional zone, in which a morphology analysis algorithm was applied in addition to rate. Each of the zones was described in detail in previous studies (2,3,5).

SAFETY. The complication-free rate methodology was consistent between studies (2,3). The entire pooled cohort was prospectively evaluated for device-related (type I) complications, labeling-related (type II) complications (i.e., events caused by the labeling, including inadequate labeling or situations where the labeling instructions were not followed), and procedure-related (type III) complications that required invasive action to ameliorate the complication. The databases collected these complications over a range of 2 to 1,542 days, including all adverse events, but we focused on mortality, infection, inappropriate shocks and battery longevity, capacitor function, and random hardware or software component failure of the implanted hardware from the day of implantation.

and St. Jude Medical. Dr. Gold has received consulting fees and research grant support from Boston Scientific, Medtronic, St. Jude Medical, and Sorin; and speaking fees from Sorin Group and Biotronik. Dr. Knight has received consulting fees, speaking fees, and research support from Boston Scientific and Medtronic. Dr. Theuns has received institutional grant support and consulting fees from Boston Scientific. Dr. Boersma has received consulting fees from Medtronic and Boston Scientific; and speaking fees from Medtronic, Boston Scientific, and Biotronik. Dr. Weiss has received consulting fees, speaking fees, and research grant support from Biosense Webster, Biotronik, Boston Scientific, Medtronic, and St. Jude Medical. Dr. Leon has received research grant support from Boston Scientific. Dr. Herre has received research grant support from Boston Scientific, Medtronic, and St. Jude Medical. Dr. Lambiase has received speaker fees and research support from Boston Scientific, Medtronic, St. Jude Medical, and UCLH Biomedicine NIHR.

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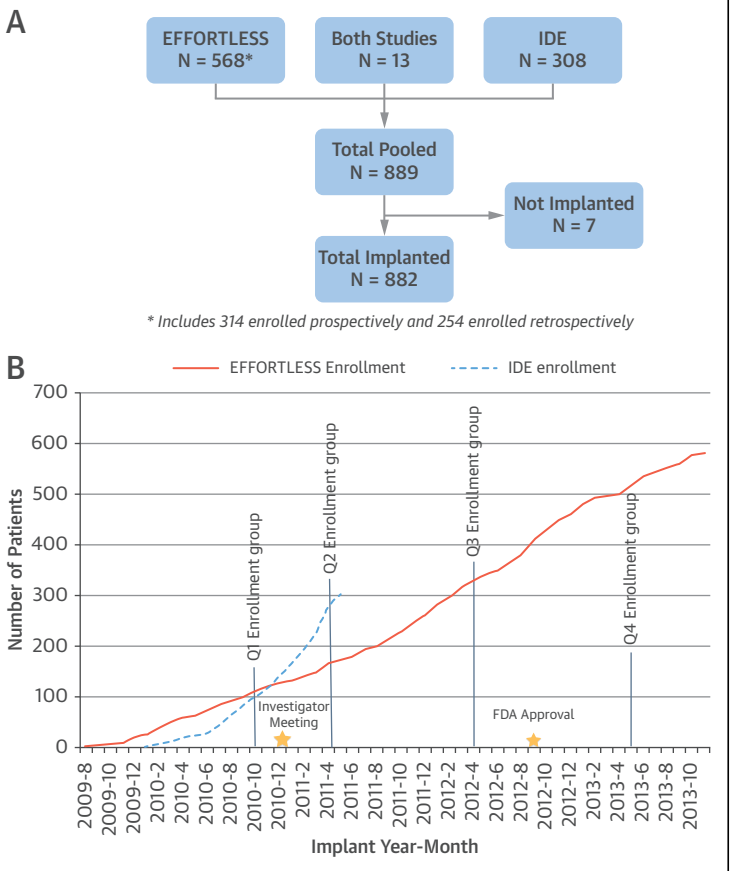
EVALUATION OF SPONTANEOUS EVENTS. Spontaneous events were defined as episodes that triggered the device to charge and store an electrogram. This required an episode to be sustained, such that the initial 18 and/or 24 beats of the tachycardia charge criterion was met. For analysis, spontaneous ventricular tachyarrhythmia (VT)/VF episodes (treated and untreated) were subdivided into 2 classes: 1) discrete episodes; or 2) VT/VF storm episodes that included 3 or more treated VT/VF episodes within 24 hours in the same patient (6). Defining these groups separately prevented the device conversion efficacy rates from being disproportionately affected by a small number of patients who experienced multiple, temporally clustered events.

Rhythm classification of treated and untreated sensed events were reported by the site, and appropriateness of therapy or detection was adjudicated by a sponsor committee (EFFORTLESS) or Clinical Events Committee (IDE). Every spontaneous stored episode was also classified as discrete or as a storm event.

THERAPY CHARACTERISTICS. Evaluation of the time to therapy for spontaneous episodes was defined from the onset of the sustained arrhythmia until a shock was delivered using electrograms produced by interrogation of the S-ICD system. Treatment outcome was defined as successful by type I termination (abrupt) or type II (gradual termination before redetection) conversion. First shock efficacy was defined as conversion of VT/VF arrhythmia before the start of a second charge. Failure to convert was defined as exhaustion of the 5 programmed therapies per event.

STATISTICAL ANALYSIS. Descriptive statistics are reported using mean ± SD, unless otherwise indicated. Kaplan-Meier analyses were used to estimate the time to first event for mortality, complications, and appropriate and inappropriate shocks. Summary statistics were also used to describe the overall rates for these events and spontaneous conversion efficacy. Study effect, which was defined as the difference in incidence rates that were significantly different between the 2 study databases, was incorporated to adjust for major differences. All statistical analyses were performed using the SAS Enterprise Guide, version 4.3 (SAS 9.3, SAS Institute, Cary, North Carolina).

FIGURE 1 Pooled Data Population



(A) A flowchart depicts the pooled cohort of study patients broken down by each contributing study. The designation **Both Studies** represents patients enrolled into both EFFORTLESS and the IDE studies. Patients **Not Implanted** underwent an implant procedure but due to high defibrillation thresholds did not leave the hospital with the S-ICD. **(B)** The staggered enrollment of both datasets of patients with the S-ICD. IDE enrollment began 5 months after the EFFORTLESS study enrollment, and it enrolled patients rapidly and early in the overall cohorts timeline. The quartiles are designated Q1 when each study met the first 100 implants; Q2 corresponds to the approximate time the IDE study met its enrollment goal; Q3 was the halfway mark between Q2 and the close of the EFFORTLESS trial patient inclusion population. Quartile distribution allowed for study effect statistical analysis between cohorts and within cohorts to place the combined data into more accurate perspective. EFFORTLESS = Boston Scientific Post Market S-ICD Registry; FDA = Food and Drug Administration; IDE = S-ICD System IDE Clinical Investigation; ICD = implantable cardioverter defibrillator; S-ICD = entirely subcutaneous implantable cardioverter defibrillator; SVA = supraventricular arrhythmia; VT = ventricular tachycardia; VF = ventricular fibrillation; US = United States; UK = United Kingdom.

RESULTS

PATIENT CHARACTERISTICS. The pooled cohort included 889 enrolled patients (detailed characteristics are listed in Table 1), 882 of whom had devices and who were followed for a mean of 651 ± 345 days (total patient-years: 1,571.5). The population was generally younger, men, and had more preserved ejection fractions than those previously reported in prospective TV-ICD trials (7–9). Primary prevention patients, patients with heart failure, coronary artery disease, atrial fibrillation, and patients with previous TV-ICDs were well represented. The primary prevention patients who had ejection fractions ≤35 accounted for 43% of the study population, and

TABLE 1 Baseline Demographic and Medical History

	Pooled IDE and EFFORTLESS Patients
Age, yrs	50.3 ± 16.9 (52.6) 7.0–88.0
Sex	
Men	636 (72.5)
Women	241 (27.5)
Height, cm	174.6 ± 10.3 (175.0) 137.0–208.0
Weight, kg	86.1 ± 22.8 (82.0) 18.0–230.9
BMI, kg/m^2	28.2 ± 6.6 (27.0) 15.2–69.0
Indication	
Primary prevention	610 (69.9)
Secondary prevention	263 (30.1)
Primary cardiac disease	
Ischemic cardiomyopathy	330 (37.8)
Nonischemic cardiomyopathy	277 (31.8)
Genetic	58 (6.7)
Idiopathic VF	40 (4.6)
Channelopathies	90 (10.3)
Other	77 (8.8)
Ejection fraction, %	39.4 ± 17.6 (34.0) 10.0–86.0
Medical history	
NYHA functional classification II–IV	327 (37.5)
Atrial fibrillation	143 (16.4)
COPD	56 (6.4)
Congestive heart failure	369 (42.3)
Diabetes	156 (17.9)
Creatinine clearance <45	34 (3.9)
Hypertension	331 (38.0)
Myocardial infarction	302 (34.6)
Stroke	45 (5.2)
Valve disease	114 (13.1)
Ablation	40 (4.6)
CABG	101 (11.6)
Previous defibrillator	120 (13.7)
Previous pacemaker	22 (2.5)
Concomitant pacemaker at implant	19 (2.2)
Percutaneous revascularization	195 (22.3)
Value surgery	53 (6.1)

Values are mean ± SD (median), range, or n (%).

BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EFFORTLESS = Boston Scientific Post Market S-ICD Registry; IDE = S-ICD System IDE Clinical Investigation; NYHA = New York Heart Association; VF = ventricular fibrillation.

together with secondary prevention patients (n = 263; mean ejection fraction: 30%), made up most of the patients who underwent implantation. Chronic kidney disease patients were enrolled. Only EFFORTLESS included patients with end-stage renal disease because the IDE study excluded them.

The majority of S-ICD patients enrolled with previous TV-ICDs presented with infection that required TV-ICD extraction (63%), with the remainder mostly experiencing failed or malfunctioned TV-ICD leads that were either removed or abandoned. Patients with a previous bipolar pacemaker were included (n = 19). These patients were screened by protocol and underwent acute conversion testing at maximum output and asynchronous mode pacing. No patients were implanted with a bradycardia device simultaneously. Patients who had an S-ICD replaced with a TV-ICD are described in the following text.

Patients who received devices for secondary prevention were in the minority (n = 263). The majority of these patients had VF or polymorphic VT as the index arrhythmia (75%), although patients with a higher VT (>170 beats/min) were included. Secondary indication patients with tachycardias that were reliably terminated with antitachycardia pacing (ATP) were excluded.

A summary of the initial S-ICD device programming is provided in Table 2. The majority of devices were programmed with 2 zones, which provided morphologic discrimination of events with rates in the conditional shock zone. Detection cutoff rates for VF were chosen at the discretion of the operator, and the median of the lowest rate zone was 200 beats/min.

There were no differences in the incidence of appropriate shocks, conversion efficacy, or mortality by study. However, a study effect was noted for a higher rate of inappropriate shocks and complications in the IDE study (early regulatory implantations) compared with the EFFORTLESS trial (post-regulatory commercial implantations).

FREEDOM FROM COMPLICATIONS. The number and type of complications throughout the follow-up period are listed in Table 3 and are illustrated in the Kaplan-Meier curve in the Central Illustration; 4.5% of patients experienced a complication within 30 days

TABLE 2 Summary of Initial Programming

Statistic/Category	Pooled IDE and EFFORTLESS Patients
Lowest rate zone	197.5 ± 19.2 (200.0) 90.0–250.0
Zones	
Dual zone	689 (79.2)
Single zone	170 (19.5)
Missing	10 (1.1)
Off	1 (0.1)
Vector	
Primary	452 (52.6)
Secondary	313 (36.4)
Alternate	94 (10.9)

Values are mean ± SD (median), range, n (%).

Abbreviations as in Table 1.

TABLE 3 All Type I to III Complications

Description	Complications	
	Events	Patients
Infection requiring device removal/revision	17	14 (1.7)
Erosion	12	11 (1.2)
Discomfort	8	8 (0.9)
Inappropriate shock: oversensing	8	8 (0.9)
Suboptimal electrode position	7	7 (0.8)
Electrode movement	7	5 (0.6)
Inappropriate shock: SVA above discrimination zone (normal device function)	6	6 (0.7)
Premature battery depletion	5	5 (0.6)
Hematoma	4	4 (0.4)
Suboptimal PG and electrode position	4	4 (0.4)
Adverse reaction to medication	3	3 (0.3)
Inability to communicate with the device	3	3 (0.3)
Inadequate/prolonged healing of incision site	3	3 (0.3)
Incision/superficial infection	3	3 (0.3)
Suboptimal PG position	2	2 (0.2)
Other procedural complications	11	8 (0.9)
Other technical complications	5	5 (0.6)
Total	108	85 (9.6)

Values are n (%).
PG = pulse generator; SVA = supraventricular arrhythmia.

and 11.1% of patients had a complication over 3 years. The 3-year Kaplan-Meier estimate for patients with a type I complication was 5.4%.

Of 108 total complications, 43 (40%) occurred in the first 30 days. Of 85 patients with complications, 14 patients had 2 or more complications (1.57% of 889 patients who underwent an implantation procedure), and 71 patients had 1 complication (7.99% of patients). Of the 14 patients with more than 1 complication, pocket erosion (n = 7) was most often associated with other adverse events. One patient had the same complication (electrode movement) twice, with no other complications. Infection and suboptimal pulse generator or electrode position were the most common complications. Suboptimal position of the electrode or pulse generator was resolved by revisions of the electrode or pulse generator; 5 of 13 events occurred during the implantation procedure, and an additional 5 events occurred within 7 days after implantation. Five device malfunctions, such as early battery depletion (0.6%) and inability to communicate with the programmer (0.3%), were very rarely seen. There were no electrode failures throughout the follow-up period or any S-ICD-related bacteremia.

Extraction of the S-ICD for pacing occurred in 4 patients (0.4%) due to the need for ventricular pacing: 1 patient developed a new bradycardia indication; 1 patient was explanted because of need for ATP; and 1 patient with 3 VT storm events underwent replacement with a TV-ICD in an attempt to suppress ventricular arrhythmias using overdrive pacing. In addition, 1 device was extracted for a cardiac resynchronization therapy upgrade.

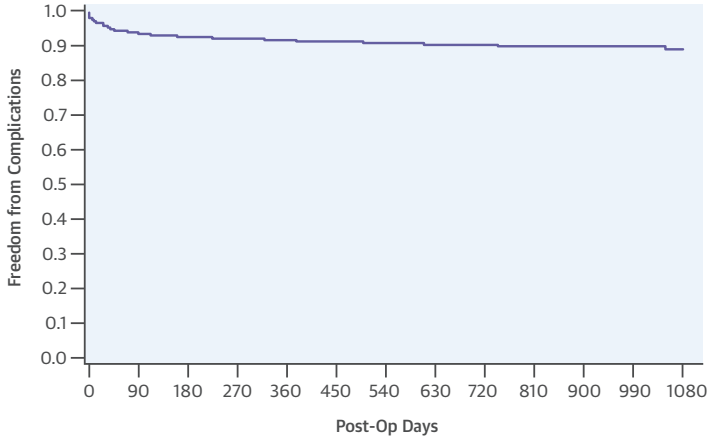
A study effect was observed for complications ($p = 0.0857$). When correcting for the time of enrollment, the effect of the study was not significant ($p = 0.5924$), which indicated that time rather than the study explained the difference in complication rates between the studies. This result is further illustrated in Figure 2A.

EFFICACY. The Kaplan-Meier incidence of time to first therapy for VT/VF was 5.3% at 1 year, 7.9% at 2 years, and 10.5% at 3 years. Excluding VT/VF storms, 111 discrete VT/VF events were treated, with 100 (90.1%) terminated with the first shock, and 109 (98.2%) terminated within the 5 shocks available. Of 51 PVT/VF episodes in 32 patients, 45 (88.2%) were converted with a single shock. Sixty monomorphic VT (MVT) episodes were recorded in 40 patients, and 55 (91.7%) were converted on the first shock. All MVT episodes were converted within the 5 shocks available. Of 2 unconverted polymorphic VT/VF episodes, 1 spontaneously terminated after the fifth shock, but beyond the time frame of the electrographic recording. In the other episode, the device prematurely declared the episode ended due to undersensing after 2 shocks. A new episode was immediately re-initiated, and the VF was successfully terminated with 1 additional shock.

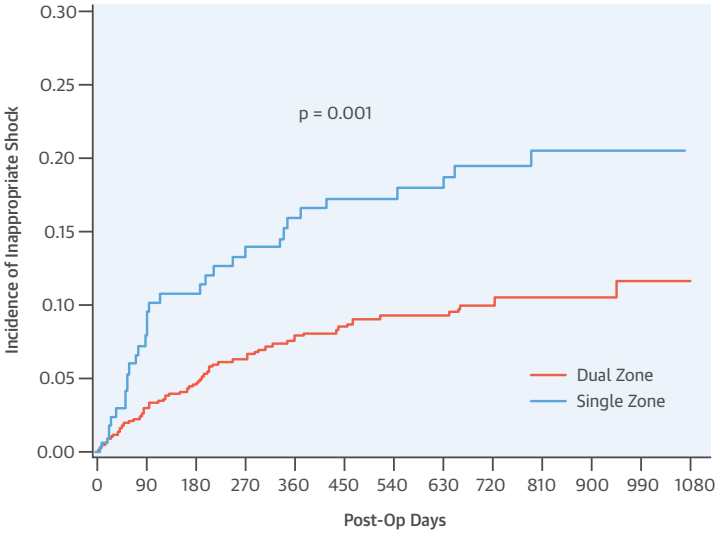
There were 12 VT/VF storms observed in 7 patients. Storm events were converted in 10 of 12 events. One of the other 2 patients received multiple S-ICD shocks for VT and was brought by ambulance to the hospital, during which time external defibrillation was also applied. Each S-ICD and external defibrillation shock resulted in conversion of the VT, followed shortly by re-initiation, until the VT was ultimately terminated by an external defibrillator shock. There was 1 previously reported patient with rare Loeffler's syndrome who experienced failed conversion of a terminal VF event subsequent to a 10-min bradycardia episode (3). This patient underwent S-ICD implantation after obliteration of the right and left ventricular apexes by a mass and was not deemed suitable for a standard ICD system (3).

A total of 104 (11.8%) patients had 314 episodes of VT/VF detected during the follow-up period where both untreated and appropriately treated VT/VF episodes in discrete and storm events were evaluated. There were 115 appropriately detected VT/VF

CENTRAL ILLUSTRATION **Long-Term Safety and Efficacy of the Subcutaneous Implantable Cardioverter-Defibrillator**



No. at Risk	878	791	731	707	650	591	525	414	303	217	162	123	105
K-M Estimate (%)	99.0	93.4	92.3	92.0	91.4	90.9	90.6	90.2	90.0	89.7	89.7	89.7	88.9

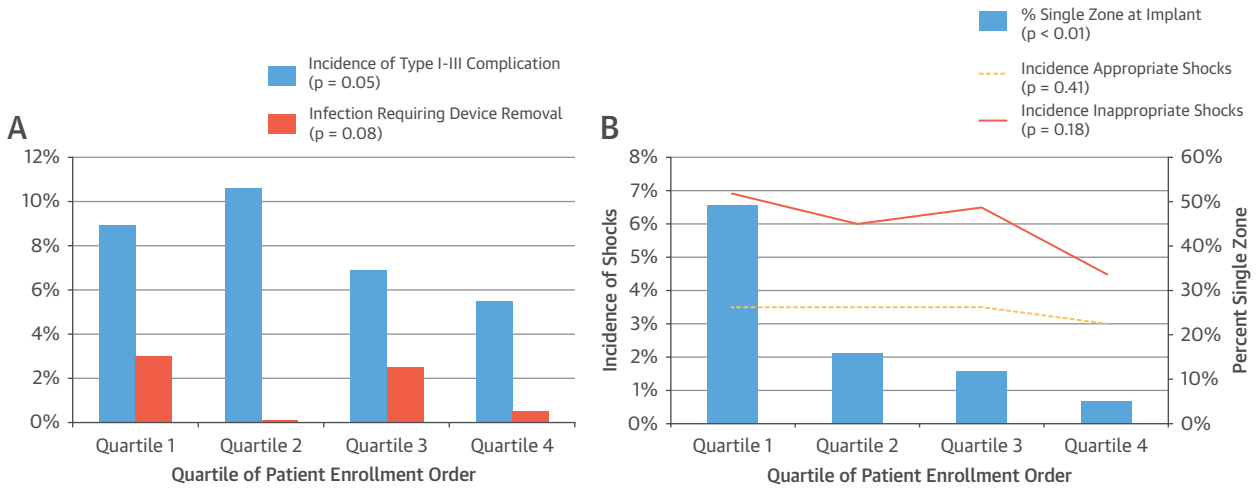


Dual Zone													
No. at Risk	688	634	576	546	494	441	378	279	180	120	89	66	56
K-M Estimate (%)	0.0	3.0	4.6	6.2	7.7	8.5	9.3	9.3	10.0	10.5	10.5	11.7	11.7
Single Zone													
No. at Risk	170	153	141	134	126	122	117	108	96	75	53	43	36
K-M Estimate (%)	0.0	7.8	10.8	13.3	15.9	17.3	17.3	18.0	19.5	20.5	20.5	20.5	20.5

Burke, M.C. et al. J Am Coll Cardiol. 2015; 65(16):1605–15.

(Top) This survival curve represents the 3-year complication-free rate for type I to III complications that require invasive action to correct. The majority of complications occurred in the first 30 days from implantation. **(Bottom)** This survival curve represents a comparison of the 3-year inappropriate shock-free rate by programmed zone. The single zone describes a shock-only zone, whereas the dual zone indicates 2 separate cutoff rates, with the lower cutoff rate including a morphology discrimination algorithm to help distinguish supraventricular arrhythmia (SVA) from ventricular arrhythmia. Dual zone programming is the preferred permanent programming due to the significantly lower inappropriate shock rate for SVA and oversensing. K-M = Kaplan-Meier.

FIGURE 2 Events by Patient Enrollment Order and Programming



(A) The 6-month incidence of complications and infections that required device removal by enrollment date. More experience with the device implant and management led to a decreased trend in overall complication and infection rates over time (Figure 1B). **(B)** The incidence of shocks (appropriate and inappropriate) by quartiles as previously described. The primary or y- axis shows the percent of patients who received an appropriate or inappropriate shock in the first 6 months, for those patients who underwent implantation at least 6 months previously (this only included patients with the opportunity to complete 6 months of follow-up). The decrease in single-zone programming shows a decrease in inappropriate shock without alterations in the incidences of appropriate shock. Other influential clinical features leading to this finding include physician experience with implantation.

episodes that self-terminated before shock delivery; 70% of these were MVTs (76 MVTs in 58 patients, 35 VFs/polymorphic VTs in 12 patients, and 4 were ventricular without site reported rhythm adjudication) compared with 199 appropriately detected episodes that were sustained long enough to require an 80-J shock. Specifically, 36 (4.1%) patients experienced events only long enough to require a shock, whereas 41 (4.6%) patients had only untreated or self-limiting VT/VF episodes. Finally, 27 (3.1%) patients had both nonsustained (self-limited) and sustained treated VT/VF episodes during the follow-up period. During the follow-up period, 1 patient's MVT burden led to the clinical decision to transition to a device with ATP capability.

The time to therapy for spontaneous episodes was 19.2 ± 5.3 s for all VT/VF therapies (MVT 18.2 ± 4.9 s; polymorphic VT and VF 20.5 ± 5.6 s). Fifteen events of syncope in 15 different patients (1.7%) were reported. Two patients with recorded untreated episodes were associated with reported syncope on the day of the episode. One event of syncope was associated with a treated episode, in which therapy was delivered for VF and required 5 shocks to convert. As mentioned previously, 1 episode of temporary undersensing was noted, but eventually cycled to terminate with a shock. All-cause mortality was 2.9% (n = 26) during the follow-up period, with only 1 known arrhythmic death (0.1%) due to Loeffler's syndrome, as described previously. The 2-year Kaplan-Meier mortality estimate was 3.2% (95% confidence interval: 1.3% to 5%), and the 3-year Kaplan-Meier estimate was 4.7% (95% confidence interval: 0.9% to 8.5%).

INAPPROPRIATE THERAPY. The Kaplan-Meier incidence of time to first inappropriate shock was 13.1% at 3 years. In patients with dual zone programming at the index procedure, the Kaplan-Meier incidence of inappropriate shock at 3 years was 11.7% compared with 20.5% with single-zone programming (Central Illustration). The majority of patients who received an inappropriate shock with either single or dual zone programming received the shock in the first year post-implantation. The causes of inappropriate shocks were supraventricular arrhythmia (SVA) above the discrimination zone in 24%, SVA discrimination errors in 1%, T-wave oversensing in 39%, low amplitude signal in 21%, noncardiac oversensing (e.g., electromagnetic interference) in 8%, oversensing of VT/VF below the rate zone in 4%, other and/or combined types of cardiac oversensing in 2%, and committed shock for VT/VF in 1%.

A significant study effect was observed for inappropriate shocks (p = 0.0209) revealing less contribution of inappropriate shocks from the EFFORTLESS study group. When correcting for the initial programmed number of zones, shock zone rate, and

conditional zone rate, the effect of the study was not significant ($p = 0.1496$).

RESULTS BY PATIENT ENROLLMENT DATE. The rate of therapy for VT/VF was similar across quartiles of enrollment in the studies (3.5% to 3.0%; $p = 0.41$) (Figure 2). The most recently implanted quartile of patients had a lower rate of inappropriate shocks at 6 months, although the trend did not reach statistical significance (Q1: 6.9%, Q2: 6.0%, Q3: 6.5%, Q4: 4.5%, $p = 0.18$), whereas there was a major increase in the use of dual zone programming from 51% to 95% ($p < 0.01$) (Figure 2B). The rate of infections requiring system explantation decreased over time ($p = 0.08$), as did the overall rate of complications ($p = 0.05$) (Figure 2).

DISCUSSION

This paper presents the largest, most comprehensive, and longest follow-up of efficacy in the treatment of spontaneous VT/VF episodes by the S-ICD to date. The main findings of the pooled cohort confirm that the favorable outcomes achieved with the S-ICD continue up to 3 years post-implantation. In addition, the rates of inappropriate shocks, infection, and overall complications improved in the most recently patients who underwent implantation.

MORTALITY. The low mortality rate in this pooled data set deserves consideration. The S-ICD annual mortality rate of 1.6% and 2-year mortality rate of 3.2% in the pooled data compares favorably with recent ICD trials. With controlled programming, the MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy) primary prevention trial had 2-year mortality rates of 5% and 7% in the high rate and delayed therapy groups, respectively (10). To date, S-ICD clinical trials have not been designed or powered to assess mortality, and care should be taken in these comparisons due to the more heterogeneous population and high cutoff detection rates in the S-ICD studies. MADIT-RIT also had high-rate therapy (>200 beats/min) that was associated with a significant reduction in mortality (hazard ratio: 0.45; $p = 0.01$) and delayed therapies that were associated with a trend toward reduced mortality (hazard ratio: 0.56, $p = 0.06$) compared with conventional programming. Conversely, the pooled data S-ICD population should have had a high risk of sudden death because this population was composed of a high percent of patients who had indications for secondary prevention (32%). Similarly, the SIMPLE (Shockless IMPLant Evaluation Trial) trial included nearly 30% of patients who required secondary prevention among 2,500 patients, but it found a higher 2-year mortality rate of 11% (11). To be fair, the S-ICD experience had younger patients (mean age 50 years) with higher ejection fractions (mean 0.39); therefore, these patients had less advanced heart failure and more functional reserve, which might be factors that explain the lower annual mortality rate. This was a provocative finding that was not prospectively powered in either study. However, it is an important aspect that deserves detailed scrutiny and longer term analysis with matched ICD populations without a pacing indication to understand a possible nontransvenous phenomenon.

INFECTION AND COMPLICATIONS. A population-based improvement in mortality with a new device is paramount, but can be negated if the implant carries a higher risk of removal due to pocket infection. Infection, without any bacteremia, remained the most common complication that required invasive action in the early experience with the S-ICD (2–4). This was also true in the pooled analysis presented in this paper. Many steps were taken to mitigate this risk, including better operative preparation training and techniques, and aggressive management of skin infections to prevent device removal (3). Advances in implantation techniques were introduced into the literature by Knops et al. (12) in an effort to decrease the incisional surface area and reduce infection risk. Advances in operator experience, preparation, and implantation technique appeared to have positively affected the rates of infection as use of the S-ICD system has expanded worldwide. The simplicity of implantation that avoided vascular access was reflected in the very low (2%) rate of acute major complications (hematoma, lead/device malpositioning/displacement) seen post-operatively versus the in-hospital major adverse events of 1.9% for single-chamber and 2.9% for dual-chamber ICDs in the National Cardiovascular Database Registry ICD Registry, respectively, including lead displacement (0.5% and 0.9%, respectively), hematoma (0.6% and 0.8%, respectively), and pneumothorax (0.3% and 0.5%, respectively) (13). The rate of major complications rose to 3.5% for single-chamber ICDs and 4.8% for dual-chamber ICDs through the first 90 days of follow-up when the National Cardiovascular Database Registry database was linked to Medicare (14). Even higher rates of TV-ICD hematomas (2.2%) and lead displacement (1.8%) were reported for ICD patients in a pooled meta-analysis of randomized controlled trials (15).

APPROPRIATE TREATMENT EFFICACY. The success of the S-ICD system in detecting and defibrillating spontaneous VT/VF events presented in this paper validates the treatment efficacy of the system. The

spontaneous VT/VF efficacy is comparable to transvenous spontaneous event conversion, with 90% success at first shock efficacy and >98% efficacy overall (15–17). First shock efficacy for spontaneous events in TV-ICDs was 83% in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (16), 89% in LESS (Low Energy Safety Study) (17), and 90% in ALTITUDE (Long term outcome after ICD and CRT implantation and influence of remote device follow up study) (18). In the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) trial, which had a more morbid population, first shock efficacy for conversion of spontaneous VT/VF was not different by dual coil (89.6%) or single coil (92.3%) leads (19), and conversion efficacy over all shocks was 97.3% to 99.6% (17,18). Earlier reports of S-ICD efficacy relied on acute and long-term-induced conversion testing to prove shock efficacy, but there was a paucity of spontaneous events to corroborate (1–3). In combination, the spontaneous event conversion efficacy and mortality data in this paper are the most important additions to the S-ICD evidence base of experience under real-life circumstances to date.

A major cause for concern against implanting the S-ICD is the possibility that patients indicated for defibrillator therapy will benefit from ATP. Patients with recurrent VT reliably terminated with ATP were excluded from both the IDE and EFFORTLESS studies (2,3). The frequency and type of such events reported in this paper suggests that the investigators selected patients appropriately; only 1 patient had the S-ICD replaced with a TV-ICD to provide ATP. In this cohort of S-ICD patients, there were 13 patients (1.4%) with more than 1 MVT episode treated, including 2 patients with storm events. This rendered an annualized rate of recurrent treated MVT of 0.8%. In a subanalysis of SCD-HeFT patients, Poole et al. (20) reported that 7% of 811 patients experienced more than 1 VT episode during the 46-month follow-up, rendering a 1.8% annual benefit for ATP. The PainfreeRx II (Pacing Fast Ventricular Tachycardia Reduces Shock Therapies) trial (21), which targeted patients with substrates for stable MVT, demonstrated a 42% reduction in shock episodes for fast VT using ATP versus shocks alone (57 vs. 99 episodes). Considering the rate of recurrent MVT in this cohort, it could be hypothesized that there was an estimated 0.3% annual benefit from ATP, or approximately 1%, if patients with any MVT were included. Due to the rapid time to therapy used at the time of SCD-HeFT and PainfreeRx II, these might be overestimates of required therapy. The MADIT-RIT study (10) showed that 22% of patients in the conventional programming arm received appropriate ATP, compared with 8% and 4% in the high rate and delayed therapy arms, respectively. Despite a difference in the rate of appropriate ATP therapy, there was no difference in patients who received appropriate shocks (5% with conventional programming or high rate programming, and 4% with delayed therapy over 1.4 years). This is comparable to our data, in which appropriate shock incidence was 5.3% over 1 year. The decrease in the appropriate episodes as implantation experience and dual zone programming increased at higher cutoff rates similar to the MADIT-RIT trial (10) are of particular interest. The S-ICD patient selection, exclusion criteria, and actual event analysis suggest a limited benefit to ATP therapy in the patient cohort presented here.

Nontreatment of self-terminating, prolonged episodes of VT/VF are as important as successfully converted VT/VF episodes. The 125 episodes of VT/VF that self-terminated without associated reports of syncope or mortality confirm the appropriateness of a more deliberate time-delayed strategy in tachyarrhythmia sensing algorithms, such as the S-ICD algorithm, to avoid unnecessary shocks.

INAPPROPRIATE SHOCK RATE. The incidence of inappropriate shocks in this pooled cohort was higher than the EFFORTLESS patients alone, and was driven by the early experience of the IDE study. Preimplantation screening methods and experience have evolved (22). Publication of the START (Head to head comparison of arrhythmia discrimination performance between subcutaneous and transvenous arrhythmia detection algorithm trial) Study and MADIT-RIT led to higher cutoff rates and dual zone programming, with significant reductions in inappropriate shocks (10,23). In this pooled analysis, dual zone programming increased from 51% to 95% and was driven by lessons learned from the START study and early implantations in the IDE and EFFORTLESS studies. The 6-month incidence of inappropriate shocks dropped by 34% from the first quartile of enrolled patients to the last quartile of enrolled patients.

The S-ICD has so far been implanted for a wide variety of indications, including many patients at high risk of defibrillation failure (hypertrophic cardiomyopathy patients, renal failure patients, and patients with post–TV-ICD infection) and in younger patients with primary electrical or structural congenital disease. The context of the appropriate and inappropriate therapies in patients with the S-ICD needs to include consideration of these broad substrates and circumstances as the use of the S-ICD system expands in such groups.

STUDY LIMITATIONS. This pooled analysis combined data from 2 separate databases with predominately prospectively enrolled patients. Combining the groups introduced a risk of bias as did the inclusion of some retrospectively enrolled patients into the pool for analysis. However, the groups were pooled because of the congruent nature of the inclusion and/or exclusion criteria of the studies, as well as the timing of their enrollment. The collection of data and analysis of complications was also consistent between the studies. Mortality comparisons to other studies are difficult due to demographic differences and lack of data on patients withdrawn from the study. EFFORTLESS allowed enrollment post-implantation, a factor that might introduce a survival bias in these patients.

CONCLUSIONS

The S-ICD showed very high shock efficacy for spontaneous ventricular arrhythmias and a decreasing incidence of inappropriate shocks. The complication-free rate and low mortality rate extended beyond the first year. The rate of inappropriate shocks and the risks of infection and total complications decreased as physicians who performed the procedure gained more experience with the device. These data provided further support for the safety and efficacy of the S-ICD in patients with primary and secondary indications without pacing indications over a 3-year period.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Automatic S-ICDs without transvenous high voltage electrodes are effective in detecting and terminating VTs and avoiding mortality in patients at high risk of sudden death; they are also associated with relatively low rates of lead failure or complications that require repeated operations. Over 3 years of follow-up, the most frequent adverse events were generator pocket infection and inappropriate shocks resulting from oversensing.

TRANSLATIONAL OUTLOOK: Further engineering enhancements and advances in dual zone programming at higher cutoff rates should be directed at decreasing inappropriate shocks.

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KEY WORDS pacing, rhythm disorders, tachyarrhythmias, ventricular fibrillation

APPENDIX For the list of investigators and institutions participating in the EFFORTLESS S-ICD Registry and IDE study, please see the online version of the article.